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Is neocortical-hippocampal connectivity a better predictor of subsequent recollection than local increases in hippocampal activity? New insights on the role of priming

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Abstract

During memory encoding, increased hippocampal activity – thought to reflect the binding of different types of information into unique episodes – has been shown to correlate with subsequent recollection of those episodes. Repetition priming – thought to induce more efficient perceptual processing of stimuli – is normally associated with decreased neocortical activity, and is often assumed to reduce encoding into episodic memory. Here, we used fMRI to compare activity to primed and unprimed auditory words in the presence of distracting sounds, as a function of whether participants subsequently recollected the word-sound associations, or only had a feeling of familiarity with the word, in a subsequent surprise recognition task. At the behavioral level, priming increased the incidence of subsequent recollection. At the neuronal level, priming reduced activity in the superior temporal gyrus (STG), but also reversed the traditional increase in encoding-related hippocampal activity associated with subsequent recollection relative to subsequent familiarity. To explain this interaction pattern, further analyses using dynamic causal modeling showed an increase in connectivity from left STG to left hippocampus specific to words that were later recollected. These findings show that successful episodic encoding is not determined solely by local hippocampal activity, and emphasize instead the importance of increased functional neocortical-hippocampal coupling. Such coupling might be a better predictor of subsequent recollection than the direction of local hippocampal changes *per se*. We propose that one consequence of priming is to “free up” attentional resources from processing an item in a noisy context, thereby allowing greater attention to encoding of that context.

Keywords: repetition priming, recognition, recollection/familiarity, hippocampus, effective connectivity.

INTRODUCTION

Episodic memory refers to recollection of contextual information associated with a prior episode, and is often associated with an autonoetic consciousness that gives rise to subjective mental time travel (e.g. Tulving, 2001; Gardiner, 2001; Eustache & Desgranges, 2008). Sometimes however, a stimulus may seem familiar, without any recollection of related contextual information; a situation related to noetic consciousness and possibly semantic memory (Tulving, 2001; Gardiner, 2001). The hippocampus is generally thought important for binding together the different types of information associated with episodic memories (for review, see Eichenbaum, 2004; Davachi, 2006). This is consistent with functional neuroimaging studies that have reported increased hippocampal activity associated with encoding processes that lead to subsequent recollection, relative to those leading only to a feeling of familiarity (e.g. Davachi, Mitchell, & Wagner, 2003; Ranganath et al. 2004; Uncapher & Rugg, 2005). Here we report a new finding - whereby an increase in hippocampal activity is not associated with subsequent recollection - and demonstrate instead the importance of increased functional coupling between hippocampus and neocortex for successful episodic encoding.

We achieved this novel finding by combining an implicit repetition priming paradigm with a subsequent explicit recognition memory paradigm. Priming normally elicits reduced activity in the cortical regions associated with processing those stimuli; a reduction that is often attributed to more efficient processing (e.g. Henson, 2003; Schacter, Wig, & Stevens, 2007). We hypothesize here that when stimuli are presented in noisy environments, priming improves their perception, and thereby also improves their binding with the concurrent context in episodic memory.

One might expect that if primed stimuli are more efficiently processed – i.e., are less novel or “surprising” – then they are less likely to be encoded into episodic memory. Indeed, one previous study showed that conditions that increase priming can impair the encoding of explicit memories (Wagner, Maril, & Schacter, 2000; though see Stark, Gordon, & Stark, 2008). However, the visual word stimuli in that study were presented under relatively good perceptual conditions. Furthermore, Wagner et al. (2000) measured subsequent recognition memory using confidence judgments which do not distinguish recollection from feelings of familiarity in the absence of episodic retrieval (Mandler, 1980). Indeed, familiarity can be strong enough for highly confident judgments (Gardiner, 2001). In a recent behavioral study (Gagnepain, Lebreton, Desgranges, & Eustache, 2008b), we used a Remember/Know/Guess (R/K/G) paradigm (Tulving, 1985; Gardiner, Ramponi, & Richardson-Klavehn, 1998) to separate recollection and familiarity of auditory words in the presence of background sounds. In addition, participants had to justify their R responses by further recalling the associated background sound (from two possible alternatives). Our results showed that though prior repetition increased the probabilities of both subsequent recollection and familiarity, the amount of behavioral priming only correlated with the probability of subsequent recollection. This supports the above hypothesis; that is, though prior repetitions can increase levels of both recollection and familiarity, priming can also specifically aid the encoding of episodic memories, by helping to bind an (impoverished) stimulus with its concurrent context.

However, the neuronal correlates of such relationship, and especially the impact of neuronal priming on hippocampal processes, are currently unknown. Here we adapted our previous paradigm (Gagnepain et al., 2008b) to fMRI, and used dynamic causal modeling (DCM) (Friston, Harrison, & Penny, 2003) to explore effective connectivity (coupling)

between the hippocampus and a region of the superior temporal gyrus (STG) that exhibits repetition suppression associated with priming of auditory words (Gagnepain et al., 2008a). The paradigm entails three distinct phases (Figure 1A): 1) an initial phase in which “primed words” were presented three times during a phoneme-detection task; 2) a second phase, twenty-four hours later, when these primed words (together with unprimed words and pseudowords) were presented during a lexical decision task with concurrent sound backgrounds and during which the critical fMRI data were acquired, and 3) a final, surprise recognition test (after removal from the scanner) for words presented in the second phase (R/K/G paradigm).

[Insert Figure 1 here]

METHODS

Participants

24 right-handed French men aged 20 to 30 years ($M = 23.5$; $S.D. = 2.9$) were paid to take part in the study. Only men were recruited to match the population sample of our previous experiment (Gagnepain et al., 2008a). They had no reported history of neurological, medical, speech or hearing disorders, had at least 14 years’ schooling and presented normal MRI structural images. The project was approved by the regional ethics committee and all participants gave written consent. Two participants were excluded from the analyses due to excessive head motion as defined by outlying standard deviations for slice-wise differences across successive scans.

Stimuli

The items, which were recorded by a female voice, comprised 520 words taken from the LEXIQUE French database (www.lexique.org), 92 pseudowords and 20 consonant sounds used during the first, phoneme-detection phase (see Procedure below). Six lists of 80 words were created according to the different experimental conditions (see Procedure),

plus one list of 40 words for the study and test training phases. All the lists were paired separately according to various criteria, including concreteness, their French text corpus frequency, Web frequency, gender, stimulus duration, and number of phonemes (5 to 8) and syllables (bi-/tri-syllabic). 24 of the various possible combinations of the six word lists were selected in a pseudorandom way, so that the experimental conditions assigned to the lists were counterbalanced across the participants.

276 sound contexts were selected from the various databases available on the Internet (Shafiro & Gygi, 2004). Three lists of 80 sounds were created in accordance with the experimental conditions, plus one list of 36 sounds for the priming test training phase. Using audio processing software, these sounds were then divided into 2-second representative temporal windows. The words and pseudowords assigned to the auditory lexical decision task were perceptually degraded by adding these sound contexts. The 3 sound lists were counterbalanced across the word lists and participants so that each sound list was associated equally often with each word list and each experimental condition. This procedure thus led to the creation of 1,440 different test stimulations for words and 240 for pseudowords. Particular care was taken to ensure that none of the word-sound associations involved any obvious semantic relations.

Procedure

First phase: priming words during a phoneme-detection task

After a short training period, the participants heard a total of 480 words and performed a phonological task designed to encourage detailed perceptual processing. After a 500-ms gap, each word was followed by a phoneme pronounced in the same voice as the target word and lasting approximately 300-600 ms. Participants were instructed to decide whether this phoneme was present in the preceding item. Positive (phoneme present) and

negative (phoneme not present) trials were counterbalanced across words and participants, and as far as possible, target sounds were located equally often at the beginning, middle and end of words. 240 of the 480 trials corresponded to the same 80 words presented three times. There was an interstimulus interval (ISI) of 3,000 ms after each participant's response. The phase was divided into three blocks of 160 trials: 80 prime words (presented once in each block), and 80 distractors (only presented in one block). All the words within a block were presented in a pseudorandom order. This three-block structure was not perceptible to the participants and was used purely for methodological purposes.

Second phase: test phase of the priming task/incidental encoding phase

24 (\pm 6) hours later, participants performed an auditory lexical decision task during a single fMRI session. 240 items were presented in 240 different sound contexts: 80 primed words, 80 unprimed words, and 80 pseudowords. Participants had to decide, as quickly as possible, whether or not the items corresponded to a word belonging to the French language. They were also told to pay attention to the sound and were given the impression that they were taking part in a study of the neuronal mechanisms involved in the perception of speech that has been degraded by sound. Participants were also instructed to close their eyes in order to focus on the auditory task. For each trial, the items started without any cue and participants' reaction times (RTs) were measured from the onset of the words. All trial conditions (primed words, unprimed words, pseudowords) were presented according to an efficient stochastic design. The ISI varied between 3,600 ms and 4,400 ms (mean = 4,000 ms, 1.82 TRs, see below), ensuring that the hemodynamic response was sampled approximately every 200 ms over the trials. Items were presented using E-Prime software run by the IFIS System Manager, controlling stimulus delivery by synchronizing each trial with a series of TTL pulses produced during imaging acquisition. Items were delivered via

an electrodynamic audio system (MR-CONFON, Magdeburg, Germany) ensuring attenuation of scanner noise by up to 45 dB.

Third phase: recognition task

Fifteen minutes after being removed from the MRI scanner, participants performed a final recognition memory test on the 160 old words (80 primed and unprimed words from the second phase) and 80 new words, with an ISI of 2,500 ms after each participant's response. In our previous behavioral study (Gagnepain et al., 2008b), we noticed some participants had difficulties recalling the sound context associated with each word, which is not necessarily surprising given that the two different sounds used were incidental to the encoding. To address this problem, old words during the recognition task were presented with the same sound contexts as during the lexical decision task. If they had accurate memories of both the word and the sound context, and if they mentally relived this stimulation, they had to reply "Yes, I remember" (R response). If, on the other hand, their positive response occurred in the absence of any mental reliving, i.e. was based on a feeling of familiarity with the word that could not be associated to the sound (even if the sound itself might be familiar), they had to reply "Yes, I know" (K response). To increase the specificity of memory traces and hence unique recollection of episodes, we used as many sound backgrounds as words rather than just two sound backgrounds. Moreover, to ensure that R responses did not solely correspond to the recollection of the sound context, new words were presented with the (old) sound contexts associated with the pseudowords and participants were informed of this fact. Lastly, if the participants had any doubts about their response, they were told to give an "I guess" judgment (G response; see Gardiner et al., 1998) and if they were sure they had not seen the word in the scanner, the instruction was to reply "No" which was labeled as Miss (M) when it was an old word.

Debriefing

In a final debriefing, participants were asked whether, during the second lexical decision phase, they had noticed that any of the words had been used in the initial (phoneme-detection) phase on the previous day. All participants noticed repetition of a few words, but only 3 participants reported noticing repetition of up to 20 words. Participants also said they did not notice any difference between these repeated words and the other words that they remembered during the subsequent memory task. Lastly, none of the participants reported using intentional encoding or retrieval strategies during the first two phases, saying that they were focused on the perceptually-demanding main task.

fMRI data acquisition

All images were acquired using a Philips 3T system (Eindhoven, Netherlands). Blood oxygen level-dependent (BOLD) images were collected using a T2*-weighted, echoplanar sequence (64x64x34; 3.5x3.5x3.5 mm³; FOV = 224 mm; TE = 35 ms; flip angle = 80°, TR = 2,200 ms). The slices were acquired in an interleaved, ascending direction. The 446 functional volumes were collected during one functional session, where the first six volumes were discarded to allow for equilibration effects. T1-weighted structural images were also acquired (256x256x180; 1x1x1 mm³; TE = 4.6 ms; flip angle = 20°; FOV = 256 mm; TR = 20 ms).

fMRI data processing

Data were analyzed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). During pre-processing, images were first corrected for slice acquisition temporal delay, before being spatially realigned to correct for motion. Images were then normalized using the parameters derived from the nonlinear normalization of individual gray-matter T1 images to the T1 template of

the Montreal Neurological Institute (MNI), and spatially smoothed using an 8-mm FWHM Gaussian kernel.

Conventional activation analyses

In the initial analysis, the resulting pre-processed time series in each voxel were high-pass filtered to 1/128 Hz, and globally scaled by the mean over all voxels at each scan. Regressors within a general linear model (GLM) for each voxel were created by convolving a delta function at stimulus onset for each condition of interest with a canonical hemodynamic response function (HRF) and its time and dispersion derivatives. For the basic test of repetition suppression, the GLM contained only three conditions: word_{primed}, word_{unprimed} and pseudoword, plus an additional regressor for incorrect lexical decisions. For tests of memory encoding effects, a fuller GLM was created with the following additional conditions for the words: R_{primed} ; R_{unprimed} ; K_{primed} ; K_{unprimed} ; G_{primed} ; G_{unprimed} ; M_{primed} ; M_{unprimed}. Note that since participants produced few G responses in primed and/or unprimed conditions, these conditions were not included in subsequent analyses, nor were incorrect responses or pseudowords. Further regressors of no interest were the six realignment parameters to account for motion artifacts. Maximum-likelihood estimates of the GLM parameters were obtained using an AR(1) plus white noise model of the error. Linear contrasts of the canonical HRF parameter estimates (activation maps) were then computed for repetition suppression (word_{unprimed} – word_{primed}) and repetition enhancement (word_{primed} – word_{unprimed}), as well as for the repetition x subsequent recognition interaction of interest: (R_{unprimed} – K_{unprimed} > R_{primed} – K_{primed}). Note the five other possible interactions resulting from the combination of our 6 main conditions (R_{primed} ; R_{unprimed} ; K_{primed} ; K_{unprimed} ; M_{primed} ; M_{unprimed}) were also computed and reported in the Supplementary Table S3.

These contrast images were then entered into a series of one-sample t-tests in a second-level analysis, with participants treated as a random effect. We used an initial voxel height threshold of $P_{uncorrected} < 0.001$ and cluster extent threshold of $k = 5$, but corrected for multiple comparisons on the height of the statistic using Random Field Theory ($P_{FWE} < .05$) within Small-Volumes (SVC) for prior regions of interest (ROI). For the main effect of repetition suppression, the functional ROIs were defined by the thresholded statistical map for repetition suppression from the independent data of our previous study on spoken word priming (Gagnepain et al., 2008a). Given that the hippocampus has been implicated in recollection (see Introduction), while the parahippocampus gyrus (PhG), particularly the perihinal cortex, has been implicated in familiarity (Henson, Cansino, Herron, Robb, Rugg, 2003; Eichenbaum et al., 2007), we used separate anatomical ROIs for the hippocampus and PhG as defined by the AAL atlas (Tzourio-Mazoyer et al., 2002). In addition, we also separated these two different memory structures according to left and right hemispheres given the dominance of the left hemisphere in spoken word processing (resulting in 4 different search volumes). Given that we had a single a priori hypotheses as to the role of priming with respect to recollection but not familiarity (i.e. hippocampus; see Introduction), and that we expected this effect to be left lateralized, we did not correct P_{FWE} values in the left hippocampus for number of ROIs. However, because we had no a priori hypotheses as to the pattern of activity that should be expected in the 3 other ROIs, we corrected P_{FWE} values in the left and right PhG, as well as in the right hippocampus, for number of ROIs. .

Effective connectivity analyses

For analysis of functional coupling, or effective connectivity, we used Dynamic Causal Modeling (DCM; Friston et al., 2003). DCM entails defining a network of a few ROIs and the forward and backward connections between them. The neuronal dynamics

within this network are based on a set of simple differential equations relating the activity in each region to 1) the activity of other regions (intrinsic connections) and 2) experimentally-defined extrinsic input (“driving input”) to one or more of the regions, and 3), most importantly, experimentally-defined modulations (“modulatory input”) of the connectivity between regions. These neural dynamics are then mapped to the fMRI time series using a sophisticated haemodynamic model of the BOLD response. The neural (and haemodynamic) parameters of this DCM are estimated using approximate variational Bayesian techniques.

Based on our working hypotheses and the results of the activation analysis, we created a three-region DCM that contained a left STG region (which showed a main effect of repetition suppression), the left hippocampus and the left parahippocampal gyrus (PhG), both of which showed an interaction between repetition priming and subsequent recognition. The three regions were fully interconnected with both forward and backward connections. The driving input entered the left STG, and was distinguished according to primed words, unprimed words and pseudowords. The main interest was in the modulatory inputs, which applied to the forward connections from STG to hippocampus and from STG to PhG. These modulatory inputs were distinguished according to R, K and M responses. Note that backward connections were not of interest because there were no interactions to explain in the STG and because we were interested into how repetition suppression modulates subsequent memory effect in the MTL and not the reverse. Nonetheless, when we did allow modulation of backward connections by R, K, M, nothing was reliable (values close to 0 in all participants). The timeseries for each region and each participant was the first eigenvariate extracted from a sphere of 4-mm radius (volume of interest, VOI), centered on the maximum of the above group activation analysis (*Group method*). These

time series were adjusted for the effects of no interest. Note that we did not include right hemisphere regions in our DCM because we did not find reliable repetition suppression in the right hemisphere, and the simple effects of recollection and priming did not survive correction in the right hippocampus (see below).

However, the maxima identified in the *Group method* might not necessarily map onto the hippocampal and PhG regions of interest in each individual. Furthermore, the closeness of these group maxima might lead to correlated time courses in the VOIs centred in these regions, given the spatial smoothness of the functional data. Therefore, to confirm the reliability of our DCM results, we also adopted a second, *Individual method* for defining the VOIs, using a combination of anatomical and functional criteria (as recommended by Stephan et al., 2007). In this method, the maxima for each participant (defined by the same contrast than the group analysis) had to 1) be located within the same individual anatomical structure (as defined by their normalised structural MRI; see Table S4 for individual coordinates) as the group maximum (i.e. STG, PhG or hippocampus), 2) be located within 2.5 times the FWHM of the smoothing kernel of the group maxima, and 3) survive $P < .08$ uncorrected (a more severe individual P threshold would have drastically reduced the number of participants). According to these criteria, 17 individual DCMs were performed.

The DCM.B matrix for the 6 coupling parameters of interest from each participant were entered into separate group level analyses for the *Group* and *Individual* methods, to assess whether they significantly differed from zero using one-sample t-tests, Bonferroni-correcting P values according to the number of coupling parameters. In addition, we tested for differences between the coupling parameters for each of the two forward connections, i.e. from the left STG to the two left MTL regions, as a function of R/K/M responses.

RESULTS

Behavioral results

Accuracy of the phoneme-detection task during the first phase was close to ceiling. Performance of the lexical decision task during the second phase showed clear priming effects from the first phase, in terms of both accuracy and reaction times (RTs): with a significantly higher proportion of correct responses [$t(21) = 2.92, P < .01$] in the primed condition ($M = 0.78$; $SD = 0.09$) than unprimed condition ($M = 0.71$; $SD = 0.09$), and significantly shorter RT for correct responses [$t(21) = 4.21, P < .001$] in the primed condition ($M = 1507$; $SD = 83.9$) than unprimed condition ($M = 1549$; $SD = 63.9$).

Performance in the final recognition phase was measured by “Pr”, the difference in the proportion of “hits” (R, K or G) given a correct lexical decision in the second phase and the proportion of “false alarms” (FA) on new words (R, K or G). Pr was greater than zero for both R judgments, [$t(21) = 11.55, P < .001$], and K judgments, [$t(21) = 5.8, P < .001$], confirming that both R and K judgments were above the chance level, but lower than 0 for G responses [$t(21) = -3.56, P < .01$]. This shows that participants mainly provided a G response on new words but not on old words presumably because they were confident of their R and K responses on old words. Paired t-tests were performed to assess the effect of priming on subsequent proportions of R, K, and G responses (means shown in Figure 1B). They showed that, while priming increased the incidence of R hits, [$t(21) = 6.57, P < .001$], it had no effect on K hits [$t(21) = 0.88$]. Note that this difference in priming across R and K responses was reinforced by a significant two-way interaction [$F(1, 21) = 6.26, P < .05$]. In addition, these tests showed a marginal trend for priming to produce fewer G responses [$t(21) = -1.88, P = .074$].

However, when recollection and familiarity (F) were estimated under independence assumptions, with $F = K/(1-R)$ (see Yonelinas, 2002), priming also increased the incidence of F responses [$t(21) = 4.25$, $P < .001$]. Therefore, we calculated individual cumulative proportions of Hits and FA for three points - R (R), R plus K (R_K) and R plus K plus G (R_{KG}) - and transformed them into Z-values in order to produce Z-transformed Receiving Operator Characteristics (Z-ROCs) for primed and unprimed conditions (see Supplementary Figure S1). Sensitivity measures (d') for each point of the individual Z-ROCs were calculated (Z-Hits – Z-FAs). The d' measure corresponds to the perpendicular distance between each point and the $y=x$ chance line, and can therefore be used to estimate the linearity and slope of the Z-ROCs. Though no significant differences were found between R and R_K points for primed [$t(21) = 0.04$] or unprimed [$t(21) = 0.97$] conditions, a significant decrease was observed from R_K to R_{KG} points in the primed condition [$t(21) = 3.9$, $P < .01$], which was also close to significance in the unprimed condition [$t(21) = 2.05$, $P < .06$]. These results indicate that 1) the linearity assumption made by both equal- and unequal-variance signal-detection models (see Wixted, 2007; Park & Yonelinas, 2007) does not hold for the present data, and 2) priming does not simply increase memory strength as the most successful unequal-variance signal-detection model would predict, in that priming does not produce Z-ROCs with a slope < 1 between R and R_K points (Wixted, 2007; Squire et al., 2007). These results imply that R/K judgments did not rely on a single memory strength, but rather on at least two distinct sources of information, meaning that the effects of priming on both recollection (R) and familiarity (F, when scored under independence assumptions) are likely to have different causes.

Finally, lexical decision RTs in the second phase were analyzed according to a 2 (primed vs. unprimed) x 3 (subsequent R hit vs. K hit vs. Miss) ANOVA. Results showed a

significant main effect of subsequent recognition [$F(1, 21) = 5.3, P < .01$] (and main effect of priming, as summarized earlier), but no interaction between repetition priming and subsequent recognition [$F(1, 21) < 1$] (see Figure 1B). The main effect of recognition reflected slower RTs for subsequent M responses relative to subsequent K hits [$t(21) = -2.28, P < 0.05$] and relative to subsequent R hits [$t(21) = -2.99, P < 0.01$], but importantly, the RTs of subsequent K and R hits did not differ significantly [$t(21) = -0.9, P = .37$]. Paired t-tests showed significant priming for all types of subsequent recognition: R [$t(21) = -3.64, P < .01$], K [$t(21) = -2.38, P < .05$], and M [$t(21) = -2.47, P < .05$].

In summary, prior presentation in the first phase 1) facilitated response times for all primed words in the second phase, regardless of how they were subsequently remembered in the third phase, and 2) increased the probability that words in the third phase would be recollected as having been presented during the second phase, and 3) increased the probability that words would be judged as familiar, at least if R/K judgments are scored under independence assumptions, but these increases in recollection and possibly familiarity are unlikely to be based on the same increase in a single memory strength, given the results of the Z-ROC analyses.

Activation analysis

We first explored the main effect of repetition priming. When thresholding the SPM for this contrast at $P < .001$, uncorrected, no voxels showed increased responses to primed relative to unprimed words (repetition enhancement). Several clusters showed reduced responses to primed words (repetition suppression, see Supplementary Table S1) however, including a cluster of 9 voxels in the inferior part of left middle superior temporal gyrus (STG) [$x = -51, y = -27, z = +3; T_{\max} = 4.15$] (Figure 2A). Given our prior findings of repetition suppression in various areas of the bilateral STG (Gagnepain et al., 2008a), we

defined a search volume based on this previous thresholded repetition suppression map (i.e., bilateral STG fROI). The current left STG maximum survived correction for multiple comparisons within this restricted functional search volume (no maximum survived correction in the right hemisphere). The results of the other main effect – that of subsequent recognition – are reported in detail in Supplementary Table S2.

We then explored how the priming effect interacted with the type of subsequent memory. Because the pattern of interaction is orthogonal to the main effect of priming, it is possible to assess these interaction effects directly by extracting the activity in the above left STG maximum that showed repetition suppression. This maximum showed no evidence that its repetition suppression varied as a function of subsequent R vs. K responses [$F(1, 21) = 0.75, P = .48$], R vs. M responses [$F(1, 21) = 0.98, P = .34$], or K vs M responses [$F(1, 21) = 1.07, P = .31$]. Furthermore, at the whole-brain level, none of the six possible pairwise, directional interaction contrasts showed reliable effects in the STG (see Supplementary Table S3). However, there was evidence in the medial temporal lobes (MTL) that the encoding-related activation associated with subsequent recollection ($R > K$) was greater for unprimed than primed trials (Figure 2A; a display of these MTL clusters on brain slices can be found in the Supplementary Material, Supplementary Figure S2). Namely, there was a cluster of 16 voxels within the left MTL that included two submaxima, one in the left hippocampus [$x = -27, y = -18, z = -12; T_{max} = 3.8$] and another in the left PhG [$x = -24, y = -21, z = -24; T_{max} = 4.6$]. The second cluster of 7 voxels had a maximum in the right hippocampus [$x = +27, y = -18, z = -9; T_{max} = 5.2$]. Given our a priori hypothesis, we defined a search volume for the left hippocampus as defined by the AAL atlas (see Methods section). Though we did not have a priori hypotheses for the left and right PhG or the right hippocampus, we also included them as search volumes but corrected

resulting P_{FWE} values for number of ROIs (effects has to survive $P_{FWE} = 0.05/3 = .0167$). The three MTL maxima described above survived correction for multiple comparisons within their corresponding search volumes (note, however, that the maximum in the right hippocampus failed to survive correction for the number of ROIs, with $P_{FWE} = 0.02$). A similar pattern of interaction, with greater encoding-related activity associated with subsequent recollection relative to items later missed ($R > M$) for unprimed than primed trials, survived small-volume correction in the left hippocampus [$x = -21, y = -12, z = -12$; $T_{max} = 3.95$]

The patterns of activity in these MTL maxima are shown in Figure 2B (note that the absolute value of the BOLD impulse response estimates cannot be estimated efficiently in the present design, i.e, the “zero” is not important here, but rather the relative differences between conditions). To further characterize in the interactions in these MTL regions, we tested the simple effects of priming (primed vs. unprimed) on subsequent R and subsequent K responses, as well as the simple effect of subsequent memory (R vs. K vs. M) on primed and unprimed items. However, because these simple effect contrasts are not orthogonal to the interaction contrast, they cannot be performed on the response estimates extracted from the above MTL maxima without biasing the associated P value (Kriegeskorte et al., 2009). To avoid such bias, the maxima of the SPMs for the simple effect contrasts must survive the same statistical threshold used for the interaction (i.e. $P_{FWE} < 0.05$ within the left hippocampus and $P_{FWE} < 0.0167$ within the three other ROIs). Here, we found that both the simple effects of repetition suppression for subsequent R responses ($R_{\text{primed}} < R_{\text{unprimed}}$) and of subsequent recognition for unprimed words ($R_{\text{unprimed}} > M_{\text{unprimed}}$) survived correction for the left hippocampal ROI. More precisely, the $R_{\text{primed}} < R_{\text{unprimed}}$ simple effect was associated with a cluster of 6 voxels [$x = -27, y = -18, z = -15$; $T_{max} = 4.00$], while the R

$R_{unprimed} > M_{unprimed}$ was associated with two clusters of 9 voxels each [$x = -27, y = -24, z = -12; T_{max} = 4.05, x = -18, y = -12, z = -12; T_{max} = 3.86$]. Note that these three clusters largely overlapped with the clusters that showed the significant interaction between priming and subsequent recognition, including the maxima of the latter. We note also that the simple effect of subsequent recollection for unprimed items ($R_{unprimed} > K_{unprimed}$) was close to surviving correction in three different maxima within the left hippocampal ROI [$x = -18, y = -9, z = -12; T_{max} = 3.49; P_{FWE} = .08; P = .0011, x = -27, y = -21, z = -21; T_{max} = 3.43; P_{FWE} = .09; P = .0012, x = -27, y = -18, z = -15; T_{max} = 3.41; P_{FWE} = .09; P = .0013$]. None of the simple effects survived correction in the three other ROIs.

Effective connectivity analysis

To investigate further the interaction between repetition suppression and memory encoding, we applied Dynamic Causal Modelling (DCM) to a fully-connected network of the STG, hippocampal and parahippocampal left-hemisphere regions identified above (see Methods). Results of the *Group method* are presented in this section while the (similar) outcomes of the *Individual method* (see Methods section) are presented in the supplementary material (Figure S3). Note that one participant in the *Group method* analysis was excluded because of outlying DCM coupling parameters (see Supplementary Material). We assumed that the driving input, which was either a primed word, an unprimed word or a pseudoword, arrived in the left STG. The MAP estimates for these driving inputs (DCM.C matrix), as expected from the activation pattern in STG, were reliably smaller for primed than unprimed words, [$t(21) = -4.2, P < .001$] (see Table S5). Of particular interest however was whether the parameters for the two forward connections, i.e. from the left STG to the two left MTL regions, were modulated by R, K, or M responses (Figure 2C). We performed one-sample t-tests to assess whether these 6 coupling parameters of interest

significantly differed from zero, and corrected P values for this number of comparisons. Results showed a significant increase in the positive coupling between the left STG and left hippocampus for R responses [$t(20) = 3.85$, $P_{\text{Bonf. corr.}} < 0.01$], but not for K [$t(20) = 1.9$, $P_{\text{Bonf. corr.}} = 0.41$] or M [$t(20) = -1.3$, $P_{\text{Bonf. corr.}} = 0.99$] responses. Note that this increase in modulatory extrinsic coupling of 0.031 for R responses (DCM.B matrix) was observed on top of a small positive intrinsic coupling (DCM.A matrix) between left STG and hippocampus (Table S6) showing that subsequent R responses are associated with a reliable increase in STG-hippocampal effective connectivity. Furthermore, the modulatory coupling was reliably greater for R than K [$t(20) = 2.7$, $P < .05$] and M [$t(20) = 3.6$, $P < .01$] responses. None of the other forward modulatory coupling parameters, e.g. from STG to parahippocampal gyrus, was significant [$ts < 1.3$]. In sum, there was evidence of an increase in effective connectivity from left STG to left hippocampus only for words that were later recollected. Note that this main outcome was replicated using the Individual method (see Supplementary Figure S3).

[Insert Figure 2 here]

DISCUSSION

As with our prior fMRI study (Gagnepain et al., 2008b), repetition priming of auditory words presented against a background sound was associated with reduced activity (repetition suppression) in the left superior temporal gyrus (STG). For the first time however, we also found that this priming significantly modulated the increased MTL activity that is traditionally associated with episodic encoding processes that lead to subsequent recollection (relative to subsequent familiarity; e.g. Davachi et al., 2003; Ranganath et al., 2003). This interaction pattern was found across three MTL regions: left and right hippocampus, plus left parahippocampal gyrus (PhG) (Figure 2B). For unprimed items, we found the traditional increases associated with successful encoding (for items

later recollected relative to those later missed, plus a trend for items later recollected relative to those later judged familiar). This was not found for primed items however; rather we found that priming produced decreased MTL responses, but only for items later recollected.

The presence of repetition suppression in the left hippocampus specific to items later recollected is a surprising result, given that priming increased the incidence of subsequent recollection. Though priming also increased the incidence of familiarity, at least when K responses were scored under independence assumptions (Yonelinas, 2002), this increase seems unlikely to be related to hippocampal activity, given that there were no reliable differences between primed and unprimed K responses in this region. We therefore hypothesized that the determinant of episodic encoding, relative to familiarity-based encoding, is not necessarily related to an increase in hippocampal local activity, as suggested by previous studies (e.g. Davachi et al. 2003; Ranganath et al. 2004; for review Davachi, 2006; Eichenbaum et al., 2007; Squire et al., 2007), but rather a change in the functional coupling between hippocampus and the neocortical regions associated with processing the stimuli that are later recollected. Using dynamic causal modeling (DCM), we confirmed this hypothesis, in that subsequent recollection was associated with an increase in the effective connectivity from the STG region to the hippocampal region. In other words, repetition suppression in the left STG was transmitted to the left hippocampus specifically for stimuli that were subsequently recollected, explaining the decreased activity for such stimuli in the left hippocampus when they had been primed. Taking together, our findings suggest that the nature of subsequent memory (i.e. recollection vs. familiarity) does not depend solely on local hippocampal activity, but the increase of cortico-hippocampal connectivity may also be important, or even necessary.

It is worth noting that a similar interaction was found in a region of left PhG. This is contrary to previous claims for a functional dissociation between hippocampus and surrounding PhG (particularly perirhinal cortex), with the latter being implicated in processes leading to subsequent familiarity rather than subsequent recollection (Davachi et al. 2003; Ranganath et al. 2004; Diana, Yonelinas, & Ranganath, 2006). Nonetheless, the peak coordinate in the left PhG was close to the intersection between the perirhinal and parahippocampal cortices, as well as close of the hippocampus itself, so could not be attributed confidently to one or other structure. Given that we did not find reliable simple effects in the PhG, nor changes in the functional coupling between STG and PhG, we focus on the claim that it is the coupling between hippocampus and neocortex that is important for binding stimuli with their context in order to enable subsequent recollection. Finally, note also that the present analyses focused on the left hemisphere, given that the effects were generally stronger on the left, and that the left hemisphere normally shows a dominance over the right hemisphere for linguistic processing. Nonetheless, the interaction between priming and subsequent recollection was also found within the right hippocampus.

It is possible that the hippocampal activation pattern associated with subsequent memory might relate not to encoding processes during the lexical decision phase (Phase 2 in our paradigm), but rather to changes occurring during the initial presentation of primed items in the phoneme-detection phase (our Phase 1). In other words, subsequent R-hits (in our Phase 3) could be better encoded than subsequent K-hits in Phase 1 rather than Phase 2. However, if this were true, we should have observed a significant difference in the amount of behavioral priming (in Phase 2) as a function of subsequent recognition (in Phase 3), and a similar difference in the amount of repetition suppression in the STG. There was no evidence for either. Furthermore, because we instructed participants to only respond with a

R judgment when they recollected the word and the sound with which it had been paired in the scanner (i.e, from the presentation of the word in the second rather than first phase), R judgments are likely to reflect encoding processes occurring in Phase 2 rather than Phase 1. Finally, if the primed words in Phase 2 that were subsequently recollected were those that were already hippocampo-dependent from Phase 1, then these items should have been remembered explicitly during Phase 2; an occurrence that our debriefing questionnaire suggests was not frequent enough to explain our results (see Methods). In summary, though the incidence of both recollection (R response) and familiarity (K/1-R) in Phase 3 may increase following priming, the effects are likely to have different causes. K responses are likely to reflect the strength of a familiarity signal, irrespective of whether the source of that signal is Phase 1 or 2. This signal is likely to be stronger for primed items, but does not seem to relate to hippocampal activity. R responses, on the other hand, do appear to involve hippocampal encoding-related activity that occurs during the lexical decision task (Phase 2), and which are specifically sensitive to the effects of repetition priming.

There is some ambiguity surrounding the mapping of R and K responses to the theoretical constructs of recollection and familiarity (e.g. Wais, Mickes, & Wixted, 2008; Wixted, 2007; Squire et al., 2007). Indeed, it has been argued that R/K/G responses simply correspond to different response criterion along a single continuum of memory strength, and so can be modelled via signal-detection theory (e.g. Dunn, 2004; Wixted, 2007). In other words, R and K responses would be the product of strong and weaker memory traces, respectively, and might not be the expression of two distinct memory processes or systems underlying recollection and familiarity. However, three main findings suggest that such a one-dimensional model might not adequately explain the present data. Firstly, the three points on Z-ROCS corresponding to R , RK , RKG criteria did not fall on a straight line,

differing reliably in their d' values. This indicates that distribution of familiarity strength of old/new items is not Gaussian, a core assumption of signal-detection theory (see Park & Yonelinas, 2007). Secondly, the most successful unequal-variance signal-detection model predicts that increasing the strength of a memory trace, via priming, should also increase variance of the strength distribution, decreasing Z-ROCs slopes (Wixted, 2007; Squire et al., 2007). However, there was no evidence that the Z-ROCs slopes for primed and unprimed conditions differed. Thirdly, one-dimensional models cannot explain the interaction pattern observed in the hippocampus, predicting instead that the strongest memory trace condition (R primed) should give rise to the greatest response in the hippocampus (see Squire et al., 2007). Note that these results do not, of course, rule out the appropriateness of one-dimensional signal-detection models for other memory data; neither do the present results indicate whether recollection is a signal-detection or threshold process (Rotello, Macmillan, & Reeder, 2004; Park & Yonelinas, 2007). Nonetheless, the present analyses suggest that R and K judgments here map onto psychologically and neurally distinct memory processes, as originally suggested by Tulving (1985).

Prima facie, the increased recollection associated with repetition priming is contradictory to the findings reported by Wagner et al. (2000). This study manipulated the lag between initial and repeated presentations of words, and found that while shorter lags were associated with greater repetition priming and greater repetition suppression in the left pre-frontal cortex, they were also associated with reduced subsequent recognition memory. Wagner et al. (2000) interpreted this in terms of reduced encoding variability in the short lag condition (Martin, 1968). However, Stark et al. (2008) argued that while lag affects priming and subsequent recognition in opposite directions - i.e. longer lag reduces priming but increases subsequent recognition - these effects are independent and occur in parallel.

Furthermore, the neural changes in the pre-frontal cortex (and behavioral priming) in the Wagner et al. (2000)'s study are somewhat difficult to interpret, because their use of the same task during initial and repeated presentations of stimuli means that their repetition effects may reflect stimulus-response learning rather than more efficient perceptual processing (e.g. Dobbins, Schnyer, Verfaellie, Schacter, 2004; Horner and Henson, 2008, 2009; Race et al, 2009). Here, we were careful to use different tasks in the first and second phases, which means that repetition suppression (in STG) and behavioral priming are more likely to reflect more efficient perceptual processing.

To our knowledge, only one previous study has performed a direct comparison of episodic encoding and priming like ours (rather than an indirect comparison via another variable like lag). This is the study by Turk-Browne, Yi and Chun (2006), who presented visual scenes twice during an indoor/outdoor judgment task, then examined subsequent recognition memory. They found that greater repetition priming and repetition suppression, in particular in the parahippocampus and the fusiform gyrus, was associated with better subsequent recognition. Though Turk-Browne et al. (2006) also used the same task during initial and repeated presentations, the regions involved in this study are less likely to reflect stimulus-response learning (Horner & Henson, 2008; Race et al., 2009). Turk-Browne et al. (2006) interpreted their findings as reflecting the fact that both implicit memory retrieval and explicit memory encoding processes benefit from selective attention. In other words, greater attention to a stimulus can increase both subsequent priming and subsequent recognition. We did not observe a modulation of repetition priming and STG repetition suppression by subsequent memory in the present study, suggesting that participants allocated similar attentional resources to subsequently remembered and subsequently forgotten words in the lexical decision task. Furthermore, neither the Wagner et al (2000)

study, nor Turk-Browne et al (2006) study, attempted to separate recollection from familiarity, for example by using Remember/Know judgments.

Another important difference between previous studies (Turk-Browne et al., 2006; Wagner et al., 2000) and ours relates to the absence vs. presence of a noisy background context (here environmental sounds). Indeed, we propose that the interaction pattern in the hippocampal activity, and in the hippocampal-STG connectivity, reflects how well the sound context was bound to words. A previous fMRI study suggested that a noisy environment might disrupt allocation of attentional resources to an item (e.g. Stevens, Hasher, Chiew, Grady, 2008). Here, we propose a complementary mechanism, according to which item properties might change attentional resources allocated to its environment. Specifically, we propose that one consequence of priming is to “free up” attentional resources from processing an item in a noisy context, allowing greater attention to, and hence encoding of, that context. In the present experiment, though participants’ main task was to make a lexical judgment as quickly as possible on the words, our instructions also encouraged them to pay attention to the sound when they could. If more attentional resources are available for the sound context because of word priming, hippocampal binding processes should be less effortful, hence decreasing the magnitude of hippocampal activity but increasing subsequent recollection at the same time. Though we do not have objective measures of context recall in the present study and that other episodic details than the sound context might have driven R responses, the behavioral results (e.g, effect of priming on recollection) are consistent with our previous behavioral study (Gagnepain et al., 2008b), which did have such an objective measurement of recollection. While further investigation will be needed to test this hypothesis, it is consistent with recent data showing that encoding processes in the hippocampus are indeed sensitive to attentional demands

(e.g. Kensinger, Clarke, & Corkin, 2003; Uncapher & Rugg, 2008). Note also that the same attentional hypothesis may also apply to the internal context generated by participants themselves (e.g. thoughts, emotions), which often forms the basis of R judgments.

Conclusion

We showed that priming elicited reduced activity (repetition suppression) in the left superior temporal gyrus (STG). For the first time, however, we demonstrated that priming also modulated the normal increase in hippocampal activity associated with subsequent recollection. Further analyses of effective connectivity revealed an increase in functional coupling from the left STG to the hippocampus for words latter recollected, explaining the decreased activity for such stimuli in the left hippocampus when they had been primed. Our findings demonstrate that, though hippocampal local changes may be important for successful episodic encoding, they do not necessarily need to be increases in activity. Rather, subsequent recollection might be better predicted by increased connectivity between the cortex and the hippocampus, whatever direction of local activity change in the hippocampus. Nonetheless, it is important to point out that these findings do not discount previous findings of increased hippocampal activity associated with successful encoding. Firstly, we observed a similar pattern for our unprimed items, which are comparable to the stimuli used in previous studies. Secondly, successful episodic encoding generally involves a recruitment of various neocortical regions in addition to MTL, which might have been positively coupled with increased hippocampal activity if this had been examined (see e.g. Grady, McIntosh, & Craik, 2003; Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005). Moreover, studies generally assess conditions under which increased subsequent recollection (and hippocampal activity) is likely to be accompanied by increased neocortical activity as well (rather than the decreased neocortical activity found here). For

instance, elaborating semantic associations between items during encoding is likely to increase neocortical recruitment that may in return trigger increased hippocampal activity (Addis & McAndrews, 2006). In summary, our findings suggest that successful episodic encoding may not be supported solely by local changes in the hippocampus, but also depends on the nature of cortical inputs reaching the hippocampus. Our findings also suggest a new critical function of priming, which is to “free up” attentional resources from the processing of item information in order to allow greater encoding of contextual information, and hence better episodic memory.

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Figures and captions

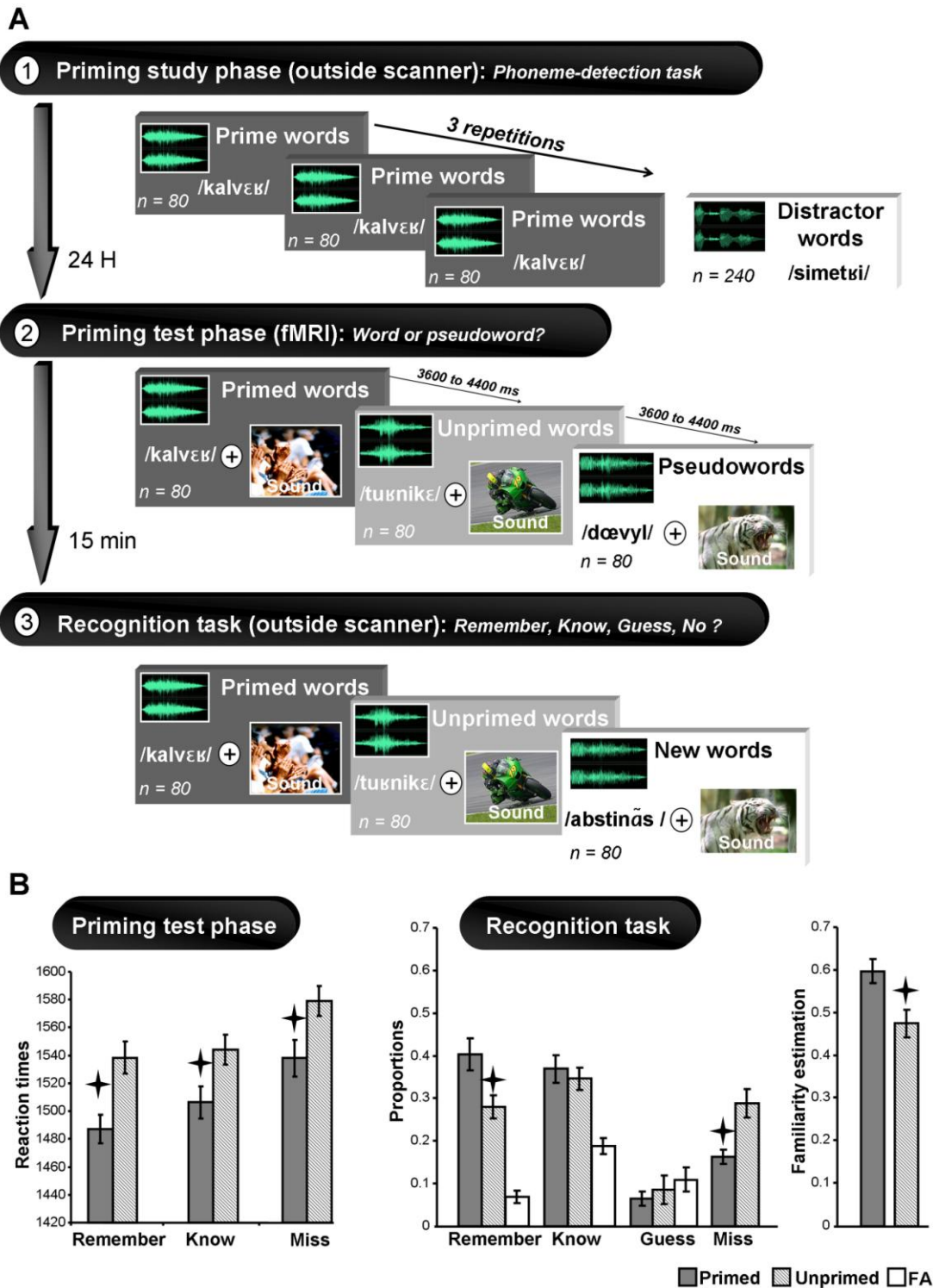


Figure 1. Paradigm and behavioral data. (A) Participants performed a phonemic processing task on the first day, in which spoken prime words were repeated three times. On the second day, brain activity was recorded by fMRI while participants heard primed words, unprimed words and pseudowords, each presented against a unique background sound, during a lexical decision task. This was followed by a final, surprise recognition task (using a Remember/Know/Guess paradigm). (B) Reaction times in the priming test phase according to repetition priming and subsequent recognition judgments (left panel). Proportions of Remember, Know, Guess and Misses according to priming, as well as proportions of false alarms (FAs) for Remember, Know and Guess responses to new items (middle panel). Proportions of Familiarity (scored under independence assumptions) according to priming (right panel). Stars represent significant differences between primed and unprimed conditions.

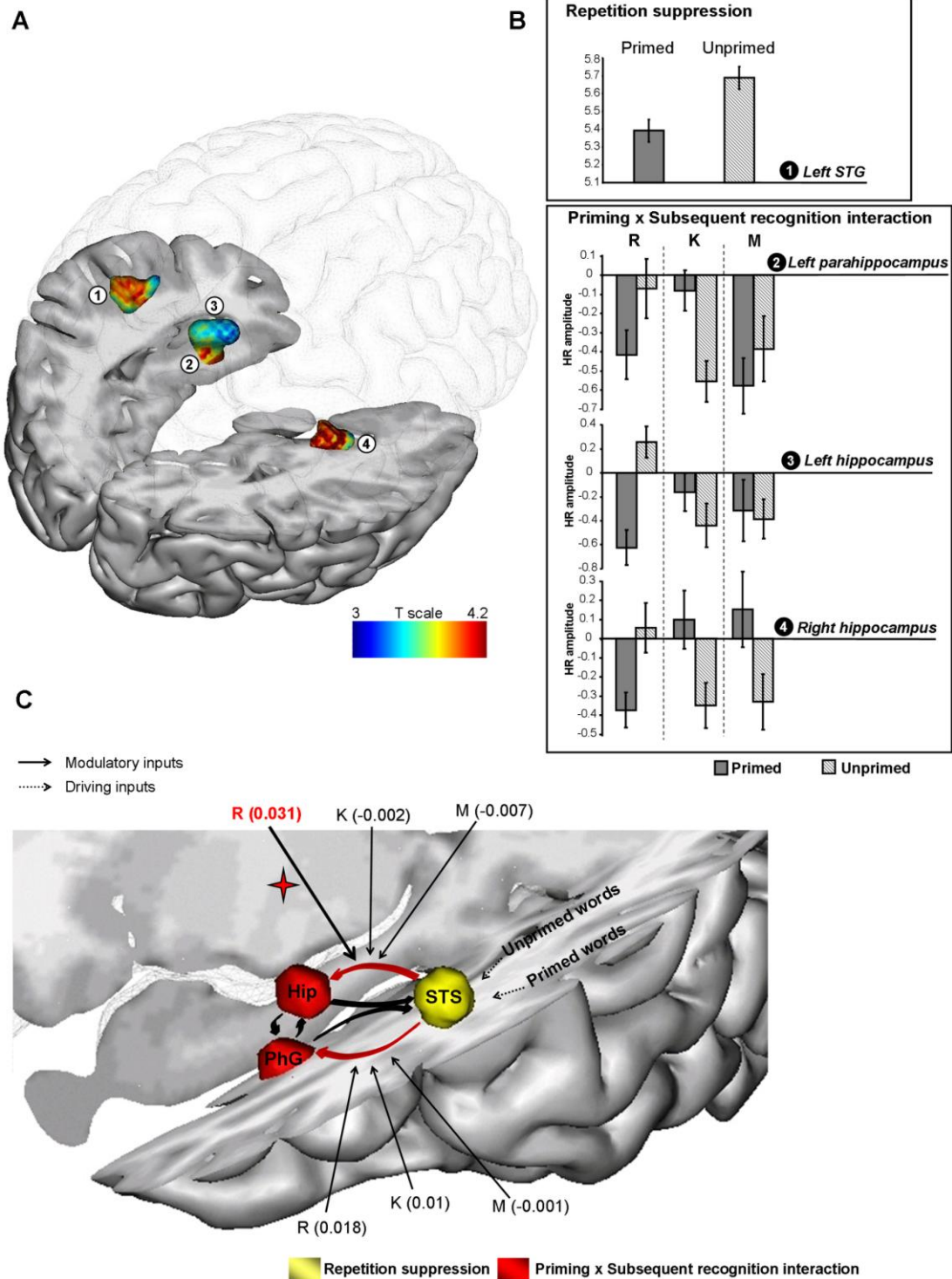


Figure 2. Results of activation and connectivity analyses. (A) Statistical parametric maps showing significant effects of repetition suppression [(1) left middle superior temporal gyrus (STG)] and of the interaction between repetition priming and subsequent recognition [(2) left parahippocampal gyrus (PhG); (3) left hippocampus; (4) right hippocampus], rendered onto a three-dimensional reconstruction of a standard brain template (thresholded at $P_{\text{uncorrected}} < 0.001$). Note that a display of the MTL clusters on brain slices can be found in Supplementary Figure S2. (B) Parameter estimates for the amplitude of a canonical hemodynamic response (HR) in the peak coordinates according to primed and unprimed words, and subsequent Remember (R), Know (K), and Miss (M) responses. Note that the pattern of responses in the peak coordinates (maxima) are presented here for display purposes, but conclusions were not drawn from statistical analyses on these data because of “double-dipping” (see Results section and Kriegeskorte et al., 2009). (C) A fully interconnected DCM model between the left middle STG, the left parahippocampal gyrus (PhG), and the left hippocampus (Hip). Primed and unprimed words entered the system as driving inputs, and subsequent Remember (R), Know (K), Miss (M) responses corresponded to modulatory inputs changing the strength of the coupling between the left STG and MTL regions (note that pseudowords were also modeled but not displayed here). Red arrows represent intrinsic connections modulated by experimental inputs. The mean coupling parameters are presented inside the parentheses. Stars represent significant effects.